# Photomediated Oxyalkynylation of Ene-carbamates and Enol-ethers with Benziodoxolone Reagents

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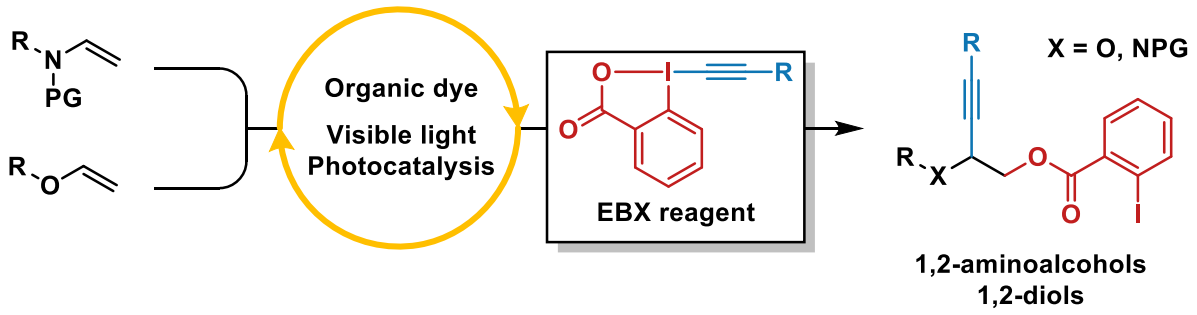
Atom economy constitutes a key point of interest for new synthetic methodologies. Alkene defunctionalisation incorporating all atoms of reacting partners is, in this context, an excellent example. It allows a rapid increase of molecular complexity, in particular in radical transformations.[1] Over the past decades, photocatalysis has emerged as a selective and efficient way to generate reactive radical intermediates.[2] In recent years, the scope of atom transfer radical additions (ATRA) to alkenes has been extended under photocatalytic conditions, allowing them to take place under mild conditions at room temperature.[3]

Alkynes have broad applications and are highly useful platforms for subsequent reactions. The development of new alkynylation strategies has become a major research topic in our group. Herein, we present a new metal-free photocatalytic method for the difunctionalisation of ene-carbamates and enol-ethers. This methodology exploits the somophilic character of the EthynylBenziodoXolone (EBX) reagents to allow the atom economical oxyalkynylation of alkenes providing acetylene containing 1,2-aminoalcohols and 1,2-diols.[4]

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# Directed Evolution of an E. coli Surface-Displayed Artificial Allylic Deallylase via the Expression of a GFP Reporter Protein

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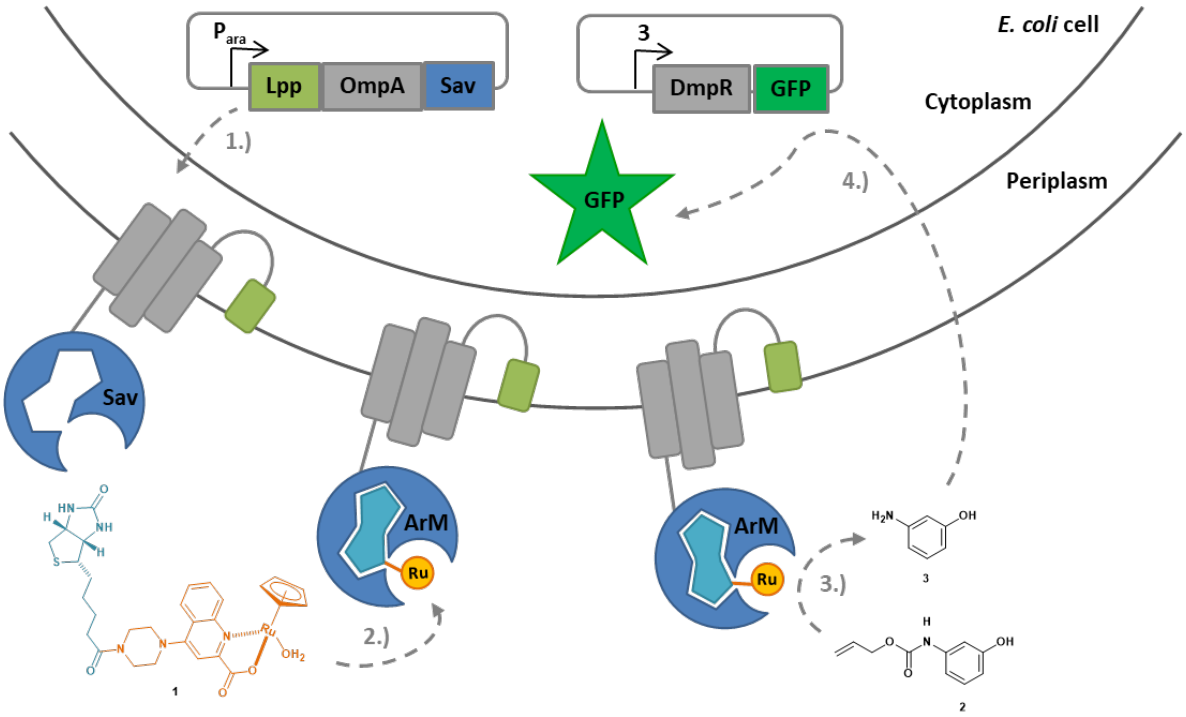
Artificial metalloenzymes (ArMs) possesses both characteristics of homogeneous catalysts and enzymes and allow the implementation of new-to-nature reactions in living organisms. [1,2] Here we present the directed evolution of an artificial metalloenzyme based on *E. coli* surface-displayed streptavidin (Sav). By addition of the ruthenium cofactor **1**, an artificial allylic deallylase is formed, which displays catalytic activity towards the deprotection of alloc-bearing substrate **2**. [3,4] The released aminophenol **3** finally triggers the expression of a fluorescent GFP reporter protein. We simultaneously saturated two amino acid residues in Sav near the ruthenium cofactor and screened 2762 individual clones. A 2.9-fold increased *in vivo* activity vs. cellular background was obtained for Sav mutant S112T-K121G. Finally, a selection of Sav isoforms was purified and for the variant S112M-K121A a total turnover number of 336 was achieved (7.1-fold increase vs. Sav wild-type). The regulation of a gene-switch by an artificial metalloenzyme allows engineering new functions into living organisms with potentially applications in biotechnology and medicine.



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# Enantioselective Methylenecyclopropanation enabled by a Dinuclear Ni(I)−catalyst

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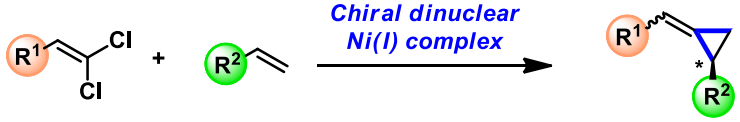
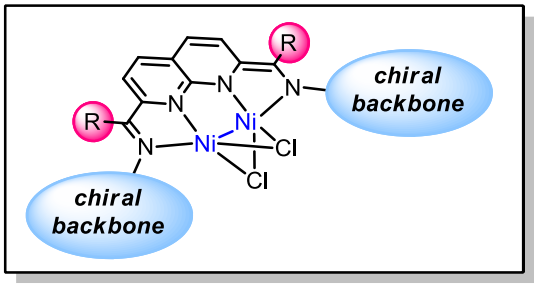
Across the diverse enzyme classes, a common motif is the remarkable use of cooperativity between two or more transition metals as a strategy for activating relatively inert substrates and mediating challenging processes. [1] The growing interest in developing multinuclear metal complexes is because they may exhibit fundamentally different properties from their mononuclear counterparts, thus allowing to access new reactivities.

Although several examples of chiral mononuclear nickel complexes are known, not many synthetic dinuclear complexes have been employed in catalysis.
In 2014 Uyeda published the synthesis of a binucleating redox−active ligand, which is capable of stabilizing dinuclear Ni(I)−complexes in five different oxidation states. [2]




Herein, we report a catalytic enantioselective methylenecyclopropanation of styrenes enabled by a novel chiral dinuclear Ni(I)−complex.

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# Copper-Catalyzed 1,2-Methoxy Methoxycarbonylation of Alkenes with Methyl Formate

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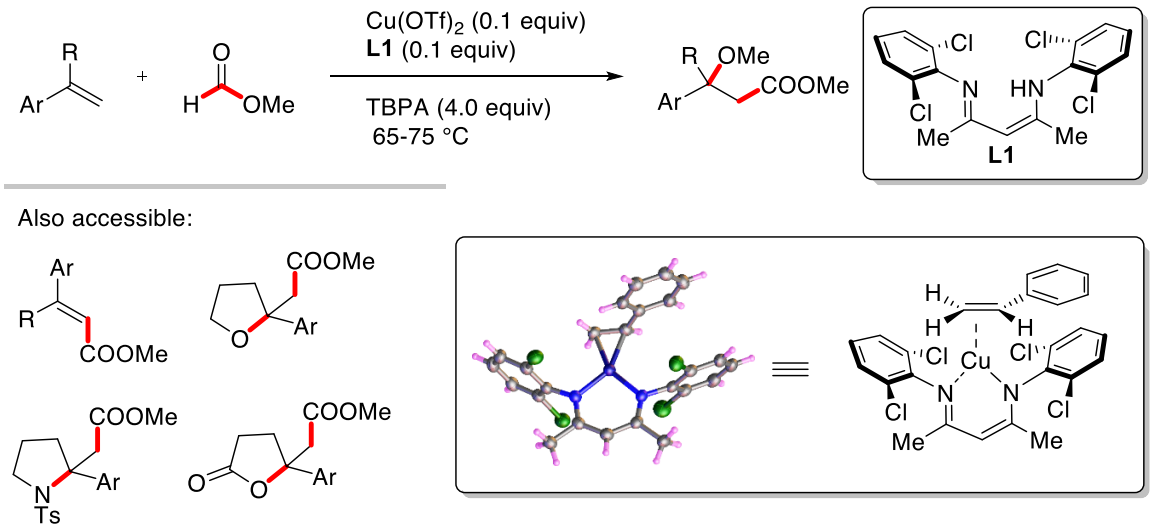
Methyl formate, an abundant commodity chemical produced over 770,000 metric tons a year, has not been exploited for the difunctionalization of alkenes. Here we report a copper-catalyzed 1,2-methoxy methoxycarbonylation of alkenes characterized by unprecedented use of methyl formate as a source of both the methoxy and the methoxycarbonyl groups.[1] This reaction transforms styrene and its derivatives, another family of bulk chemicals, to value-added β-methoxy alkanoates, cinnamates as well as medicinally important five-membered heterocycles such as functionalized tetrahydrofurans, γ-lactones and pyrrolidines. A ternary β-diketiminato-Cu(I)-styrene complex, fully characterized by NMR spectroscopy and X-ray crystallographic analysis, is capable of catalyzing the same transformation. Our finding suggests that pre-coordination of electron rich alkenes to copper might play an important role in accelerating the polarity mismatched addition of nucleophilic radicals to electron-rich alkenes and could have general implications in the design of novel radical-based transformations.

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# Rh(III)-Catalysed C-H (Hetero)arylation of Pyridones and Quinolines with IndoleBX.

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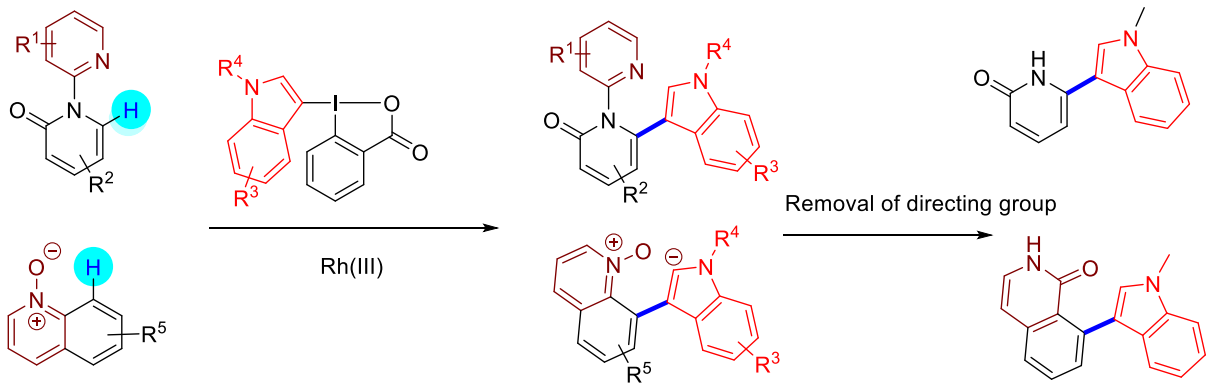
Indole heterocycles have been found in a diverse range of biologically active compounds and natural products.[1]Recently, our group developed IndoleBenziodoXolones (IndoleBX)[2] as useful reagents for the efficient transfer of indole moieties. The indole moiety can be installed through directed C-H bond functionalization under Rh(III) catalysis on N-pyridyl pyridines and quinolone N-oxides[3]. This new reaction showed tolerance towards a broad range of functional groups and was highly regioselective (functionalization of C-6 for N-pyridyl pyridines, and C-8 for quinoline N-oxides). Upon removal of the directing groups, indole-containing pyridones and isoquinolones products could be easily obtained.

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# Phenylcarbonates as electrophiles in DNA templated reactions

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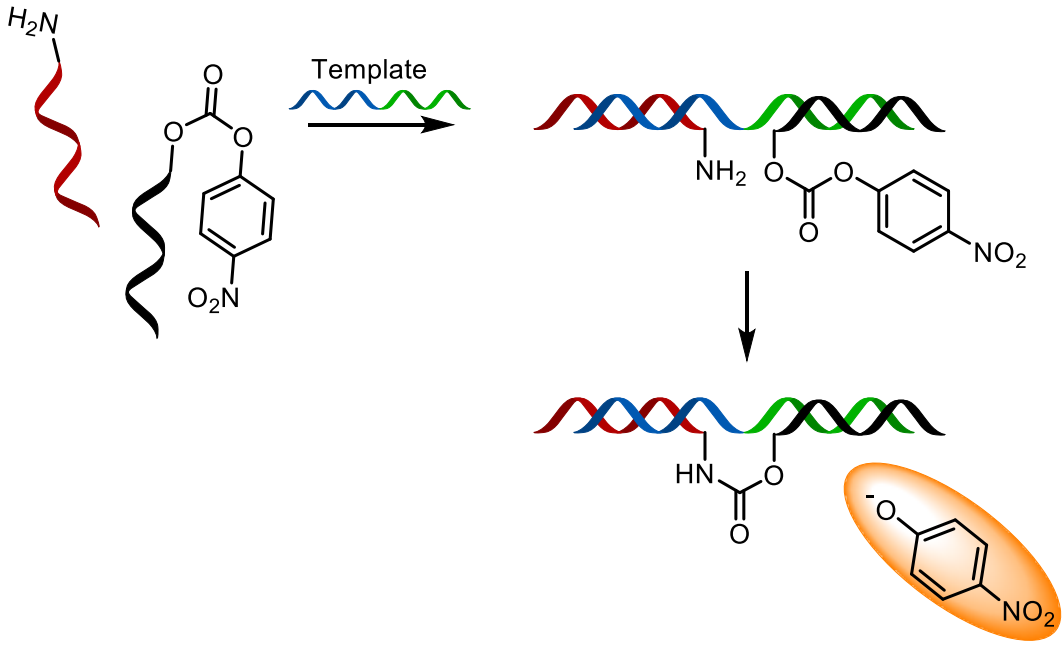
Nucleic acid templated reactions exploit the ability of nucleic acids to bind specifically to their complementary sequence, even at very low concentrations. The supramolecular interactions between two strands produce a highly pre-organized system that can be useful for synthetic chemistry or biosensing applications.[1]
Our research focuses on phenylcarbonates as reactive entities in DNA templated reactions. The carbonates are attached to DNA strands by "click" chemistry and used as electrophiles in amine/carbonyl reactions. Templation by DNA allows the reaction to take place at micro- or nanomolar concentrations.




When a reaction occurs, a reporter molecule such as a yellow coloured nitrophenolate or a fluorescent coumarin can be released, allowing an easy reaction monitoring. For systems where a ligation occurs, a successful reaction can also be showcased by denaturing polyacrylamide gel electrophoresis.

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# Visible light mediated enantioselective formation of all-carbon quaternary centers on acyclic systems

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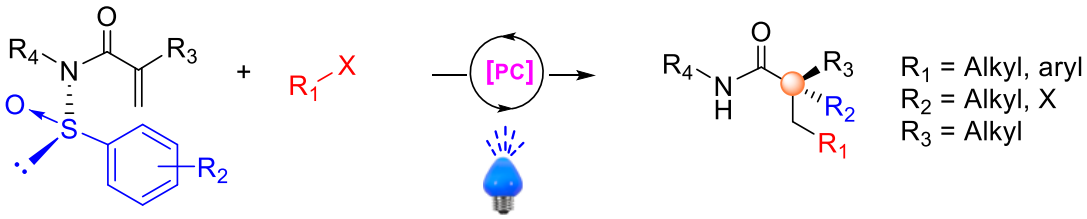
The enantioselective synthesis of all-carbon quaternary stereocenters within acyclic systems represents a major challenge for synthetic chemists. Strategies involving both single or multiple C-C bond-forming events per chemical step have been developed but sensitive reagents and careful temperature control are typically required. [1,2,3,4] Here, we present the enantioselective synthesis of α-aryl-β-substituted amides bearing an all-carbon quaternary center. The reaction proceeds via radical cascade Smiles rearrangement triggered by the photoredox catalyst. In this process, a sulfoxide group serves as a chiral auxiliary being removed during the reaction. This novel method allows the production of a wide variety of derivatives not only in good yields, but also excellent levels of stereospecifity.




**• Dual role of sulfoxide group: Chirality at sulfur controls absolute configuration / Traceless reagent**
**• Soft reaction conditions • Stereospecific method • 36 examples, 37-95% yields, up to 99:1 *er***

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# Catechol-Mediated Hydroalkylation of Electron-Rich Alkenes

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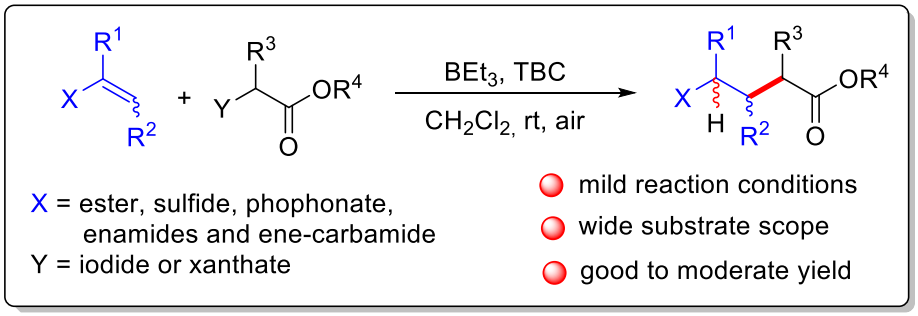
Radical chemistry emerges in recent years as a powerful method for the C-C bond formation. It allows the quick assemblage of complex structures.[1] As for the hydroakylation of alkenes, while most of the reports involve electron-poor alkenes,[2] the hydroalkylation of unactivated or electron-rich olefins are less documented. Recently, Renaud *et al.* reported the hydroakylation of mono- and polysubstituted unactivated alkenes using TBC (*tert*-butylcatechol) as the hydrogen source in the presence of air/triethylborane as the radical initiator.[3] Herein, we developed the hydroalkylation of electron-rich alkenes. It is noteworthy that stereoselective hydroalkylation was achieved by adopting chiral oxazolidinone auxiliary.

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# Surface Based Peptide Synthesis

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One of the most appealing application of this strategy is synthesis of combinatorial libraries of compounds on solid surfaces, in particular the DNA chips, where different sequences of oligonucleotides are spatially localized at different spots in the chip. These libraries are commonly prepared by initially covering the chip with the first nucleotide bearing a photocleavable protecting group, which is removed at the specific position by exposing the whole chip to UV light through a cover. At this point the deprotected spots are connected with the next nucleotide bearing themselves a photocleavable protecting group via classical reagents. Herein we want to invert the strategy, the connection of the next monomer to the growing chain will proceed directly with localized irradiation (laser or UV-LED source) through a pinhole as shown in the Figure 1.

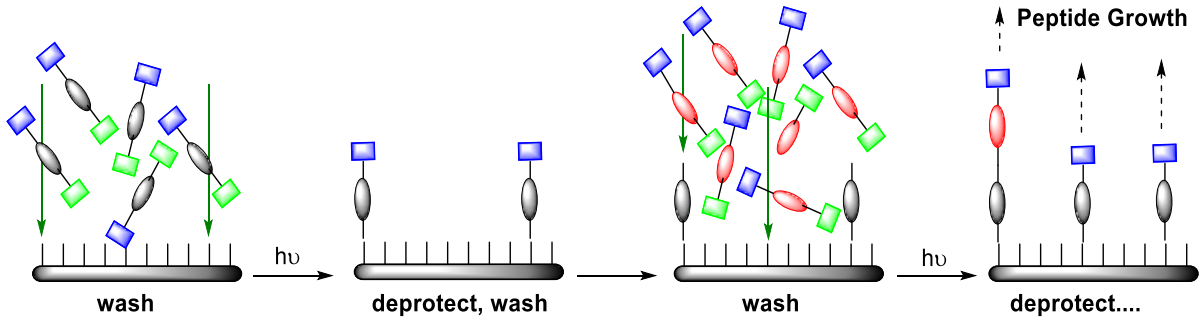


**Figure 1: Surface based peptide synthesis**

Each monomer bears from the start a photocleavable protecting group in one terminus and a classical protecting group in the other terminus. With this strategy one can have access to the desired chemistry in any given sequence at any time at any spot on the chip, because all the events are localized and independent of each other. The peptide analogous of DNA chips are called ProtoArry,® and they have been used in profiling protein-protein interaction, immune response biomarkers, small molecules, enzyme substrates antibody specificity.

# 1-Acyl Triazenes: Synthesis and Reactivity

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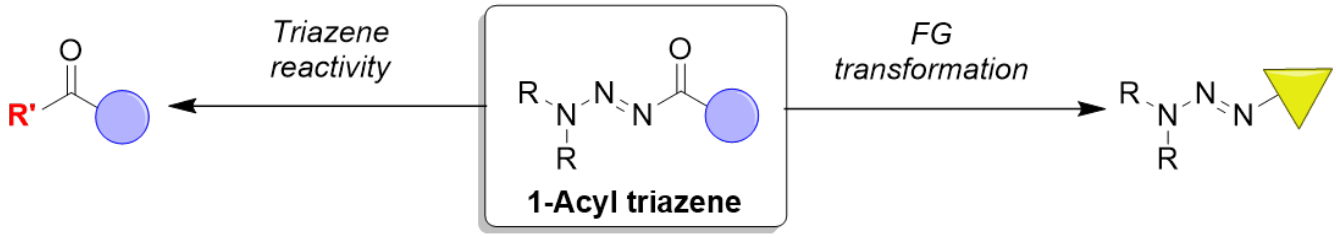
3-Acyl triazenes are well-studied compounds with applications in medicinal and synthetic chemistry [1,2]. In contrast, there are hardly any reports about triazenes with acyl groups attached to the N1 atom, and general methods to prepare these compounds are missing. Here, we show that 1-acyl triazenes are readily accessible by acid-catalysed hydration of 1-alkynyl triazenes, or by gold- or iodine-catalysed oxidation of 1-alkynyl triazenes [3]. Crystallographic analyses show that 1-acyl triazenes are characterized by very short N2-N3 bonds. 1-Acyl triazenes display high thermal and hydrolytic stability, and tolerate oxidative and strong basic conditions. Under strong acidic conditions, 1-acyl triazenes acts as acylation reagents. This reactivity could open-up new pathways for organic synthesis. In addition, functional group transformation of 1-acyl triazenes could lead to building blocks that enable late-stage functionalization.

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# Discovery of a New Acetylated Lysine Mimic and Optimization of CBP/P300 Bromodomain Inhibitors

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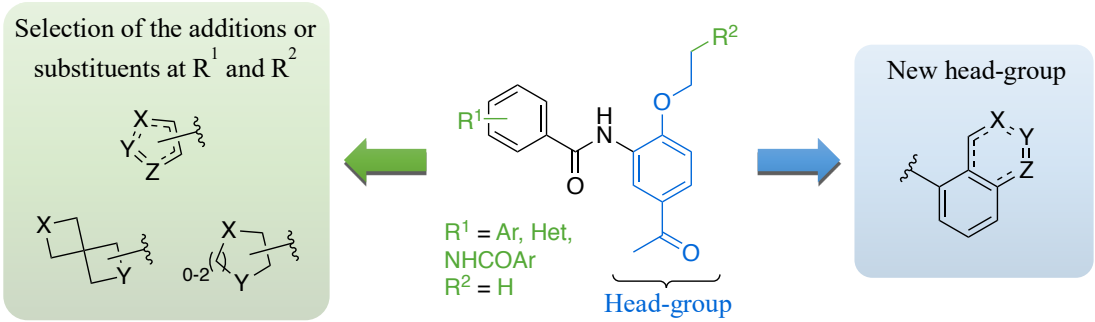
Bromodomains play a key role in the complex epigenetic regulation processes as "reader" modules of acetylated lysine residues on histone tails. This leads to a signaling cascade to activate the transcription and expression of genes.[1] Highly homologous CBP and P300 bromodomains have recently received significant interest due to their important role in the development of various human cancers.[2] However, their specific biological functions remain elusive. Orthosteric inhibitors of CBP/P300 bromodomains could further clarify the roles of these proteins in promoting disease.

Previously we reported CBP/P300 inhibiting chemical probes, bearing a *p*-ethoxy-acetophenone head-group that mimics the endogenous acetylated lysine.[3,4] Extensive optimization efforts afforded lead compounds with low-nanomolar potency, exquisite selectivity over related proteins and adequate metabolic stability and toxicity profiles. However, critical solubility issues and lack of cellular target engagement prevented further *in vivo* development of these molecules.

In this work, we examined various strategies to address these challenges, including the addition of solubilizing moieties, substitution patterns prone to disrupt planar conformations and an increase in the amount of $sp^3$ carbon atoms. Significant improvements could be achieved without sacrificing the potency of our probes.

In addition, via *in silico* high-throughput fragment-docking, a new head-group has been discovered, furnishing an improved potency and solubility compared to the previously reported *p*-ethoxy-acetophenones.

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# Iron-catalysed Remote C($sp^3$)-H Azidation of *O*-acyl Oximes and *N*-acyloxy Imidates: Synthesis of γ-azido Ketones and β-azido Alcohols

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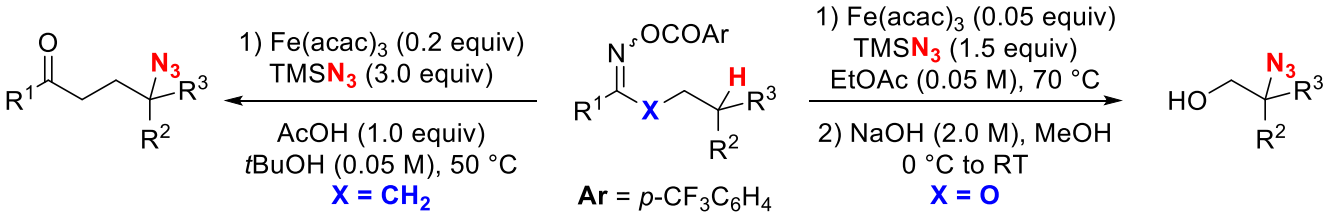
Azides are important and versatile building blocks in synthesis, allowing a fast access to an array of different functionalities[1] (e.g. amines, triazoles), notably highlighted by their use in bioconjugation[2][3]. Under the action of a catalytic amount of iron(III) acetylacetonate [$Fe(acac)_3$], various ketoxime esters and *N*-acyloxy imidates were reacted with trimethylsilyl azide ($TMSN_3$) achieving a new access to γ-azido ketones and β-azido alcohols[4].




This novel remote C($sp^3$)-H bond azidation occurred following a sequence of reductive generation of iminyl or imidate radical, 1,5-hydrogen atom transfer (1,5-HAT) and iron-mediated redox azido transfer to the translocated carbon radical. In this unprecedented transformation, the iron catalyst does not only act as a reductant for the generation of the key radical intermediates but also as a platform to promote the redox transfer of the azido moiety. This methodology was successfully applied to the synthesis of a huge variety of γ-azido ketones and β-azido alcohols in moderate to excellent yield.

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# Bisfunctionalised cationic [4]helicenes: tuning the optical properties of colourful dyes

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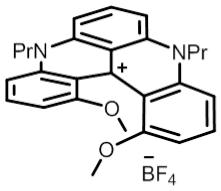
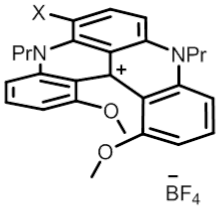
Organic aromatic helicenes commonly possess key photophysical features, like absorption, fluorescence and electronic circular dichroism (ECD) properties, that make them potential candidates for bio-imaging and optoelectronic applications. [1] Previously, an efficient tuning of the optical properties of original cationic [4]helicene **1** was achieved through regioselective post-functionalisation on the "northern region". Electron-withdrawing groups generally shifted absorption maxima and emission towards higher energies while enhancing the fluorescence quantum yields. Conversely, electron-donating groups bathochromically shifted the absorption maxima and emission towards the red. [2]

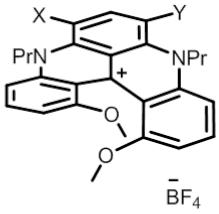



**1**




**2**

**X = $NH_2$, $NMe_2$, $NO_2$, $COO^-$, CHO**




**3**

**X = $NH_2$, $NMe_2$, $NO_2$**

**Y = $COO^-$, CHO**

In this present work, non-symmetrical disubstituted [4]helicenes have been prepared. Herein, we report comparison between the optical properties of mono **2** and bis **3** functionalised cations to establish some trends in the electronic influence of the substitution pattern on the absorption and emission properties, disclosing new perspectives for these aromatic dyes.

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# CpRu-catalyzed multicomponent synthesis of polyheterocycles through cycloadditions and metal-carbene addition

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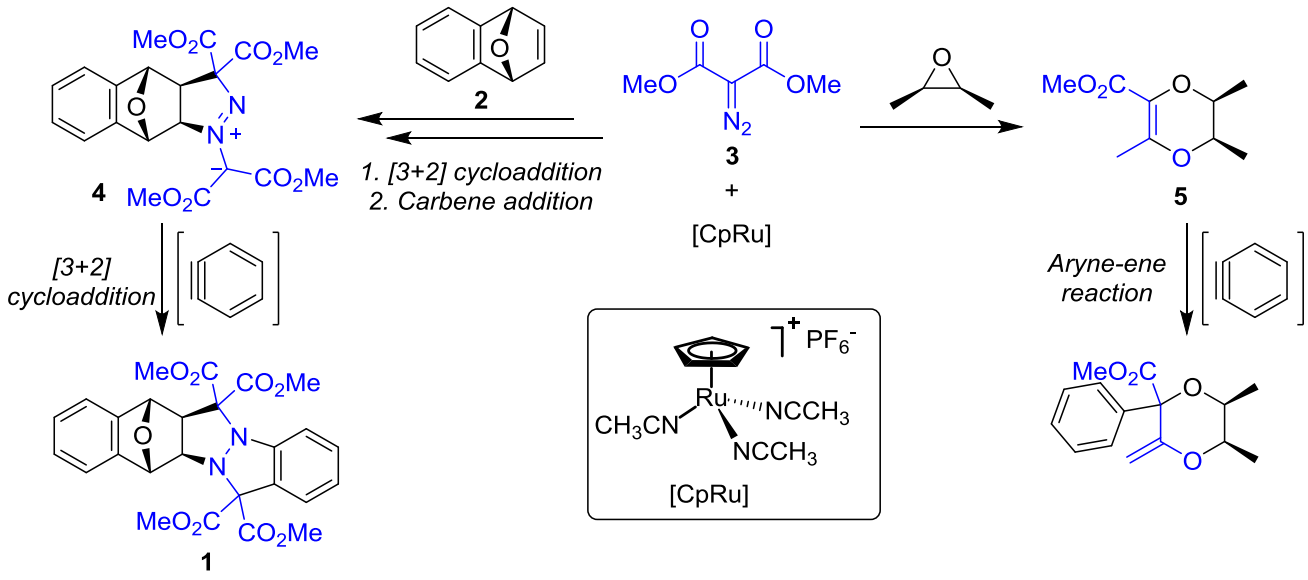
Complexes of $[CpRu(CH_3CN)_3][X]$ (X = $PF_6$ or $BAr_F$) and diimine ligands are known to promote diazo decomposition. It has been reported that such [CpRu] combinations efficiently catalyze the decomposition of α-diazo-β-ketoesters. The generated electrophilic metal-carbenes form ylides in presence of various Lewis basic substrates, such as cyclic ethers, ketones, lactones and lactams. Subsequently, the reactive intermediates undergo different rearrangement or insertion reactions.[1]

Herein, we report the one-step synthesis of diaza polycyclic compounds of type **1** by a specific combination of bicyclic ether **2** and diazomalonate **3** under [CpRu] catalysis *via* a four-component cascade involving 1,3-dipole generation and [2+3] cycloadditions. Interestingly, all postulated intermediates can be synthesized and isolated independently. Various reactions of intermediate **4** will be presented, including that with arynes. Reactivity of benzyne with dioxenes of type **5** will be also briefly considered.

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